REMARKS

Claims 19, 28 and 30 are pending in the subject application. Applicants have hereinabove cancelled claim 30 without prejudice or disclaimer to their right to pursue the subject matter of this claim in this or a future application. In addition, applicants have hereinabove amended claim 19. Support for this amendment may be found *inter alia* in the specification at page 103, lines 31-33; and cancelled claim 30. The remaining changes to claim 19 introduce minor format changes. Applicants maintain that these amendments do not involve any issue of new matter. Therefore, entry of these amendments is respectfully requested such that claims 19 and 28 will be pending and under examination.

Claim Rejections Under 35 U.S.C. §103

Claim 19

The Examiner maintained the rejection of claim 19 under 35 U.S.C. §103 for the reasons previously set forth in the February 3, 2005 Office Action issued in connection with the subject application.

The Examiner stated that applicants' argument that the cited references do not render the claimed invention obvious because the combined teaching would not have lead one of ordinary skill in the art to reasonably expect that an anti-Her-2/neu antibody could be used to treat androgen-independent prostate cancer has been considered but has not been found persuasive because applicants argue limitations not recited in the rejected claim as currently constituted. The Examiner stated that in particular, claim 19 is drawn to treatment of prostate cancer and does not mention hormone state.

In response to the Examiner's rejection, applicants respectfully traverse and note that claim 19, as amended, addresses the issues set forth above by the Examiner.

In addition, applicants maintain that the Examiner has failed to establish a *prima facie* case of obviousness against the rejected claims.

Claims 19, as amended, provides a method for treating a subject afflicted with *androgen-independent* prostate cancer, wherein the prostate cancer is characterized by prostate cancer cells which overexpress Her-2/neu protein, which method comprises administering to the subject (i) a therapeutically effective amount of a humanized monoclonal antibody which selectively binds to an extracellular domain of the Her-2/neu protein in conjunction with (ii) a therapeutically effective amount of an antitumor chemotherapeutic agent, wherein treatment with the monoclonal antibody and the chemotherapeutic agent inhibits prostate cancer cell growth more than treatment with either the monoclonal antibody alone or the chemotherapeutic agent alone.

To establish a *prima facie* case of obviousness, the Examiner must demonstrate three things with respect to each claim. First, the cited references, when combined, teach or suggest each element of the claim. Second, one of ordinary skill would have been motivated to combine the teachings of the cited references at the time of the invention. And third, there would have been a reasonable expectation that the claimed invention would succeed.

Applicants maintain that the references cited against the rejected claims fail to support a *prima facie* case of obviousness, in that they would have failed to motivate one of

skill in the art to combine them at the time of the invention.

Again, applicants maintain that the combination of the cited references does not render the claimed invention obvious because the combined teaching would not have lead one of ordinary skill in the art to reasonably expect that an anti-Her-2/neu antibody could be used to treat androgen-independent prostate cancer. In fact, the art teaches away from the use of an anti-Her-2/neu antibody to treat androgen-independent prostate cancer. As the Examiner previously pointed out, Craft et al. teach that samples from radical prostectomy, generally done at the time of diagnosis, rarely contain androgen-independent prostate cancer. The Examiner also pointed out that Myers et al. teach that increased expression of c-erbB-2 represents an early event in development and progression of prostate cancer, which according to Craft et al. is associated with androgen-dependent prostate cancer. For that reason, one of skill in the art would not expect increased expression of Her-2/neu in androgen-independent prostate cancer. Therefore, applicants maintain that the need to combine an anti-Her-2/neu antibody and an antitumor chemotherapeutic agent such as paclitaxel could not be suggested by the references. Accordingly, the cited references cannot be said to render the claimed invention obvious because there was no reasonable expectation of success in performing the claimed method for treating androgen-independent prostate cancer using a combination of an anti-Her-2/neu antibody and an antitumor chemotherapeutic agent such as paclitaxel.

Accordingly, the Examiner has failed to establish the *prima facie* obviousness of claim 19 over these references.

In view of the above remarks, applicants maintain that claim 19

satisfies the requirements of 35 U.S.C. §103(a) and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Claims 19 and 28

The Examiner maintained the rejection of claims 19 and 28 under 35 U.S.C. §103 for the reasons previously set forth in the February 3, 2005 Office Action issued in connection with the subject application.

The Examiner stated that applicants made the following arguments: (i) without experimentation, one of ordinary skill cannot reasonably predict that a successful anti-cancer outcome will occur using a particular combination of two drugs, even though each drug, when used individually has anti-cancer effects; (ii) in studies of patients with stage IV renal cell cancer, researches found that attempts to combine known renal cancer fighting drugs, i.e. Proleukin and alfa interferon have been unsuccessful and points to Exhibit B, an overview of Stage IV Renal Cancer; and (iii) based on this evidence, each specific combination of two of more anti-cancer agents must be tested before one of skill in the art can know that such a combination will be effective against cancer, let alone more effective than either agent alone. The Examiner stated that the arguments have been considered but have not been found persuasive because applicants argue limitations not recited in the claims as currently constituted, i.e. applicants are not claiming either an additive or synergistic effect.

In response to the Examiner's rejection, applicants respectfully traverse and note that claim 19, as amended, addresses the issues set forth above by the Examiner.

In addition, applicants maintain that the Examiner has failed to establish a *prima facie* case of obviousness against the rejected claims.

Claims 19, as amended, provides a method for treating a subject afflicted with androgen-independent prostate cancer, wherein the prostate cancer is characterized by prostate cancer cells which overexpress Her-2/neu protein, which method comprises administering to the subject (i) a therapeutically effective amount of a humanized monoclonal antibody which selectively binds to an extracellular domain of the Her-2/neu protein *in conjunction with* (ii) a therapeutically effective amount of an antitumor chemotherapeutic agent, *wherein treatment with the monoclonal antibody and the chemotherapeutic agent inhibits prostate cancer cell growth more than treatment with either the monoclonal antibody alone or the chemotherapeutic agent alone.*

Applicants maintain that the references cited against the rejected claims fail to support a *prima facie* case of obviousness, in that they fail to create a reasonable expectation of success.

Applicants further maintain that without experimentation, one of ordinary skill cannot reasonably predict that a successful anti-cancer outcome will occur using a *particular combination of two drugs*, even though each drug, when used individually, has anti-cancer effects. For example, in studies of patients with stage IV renal cell cancer, researchers have found that attempts to combine known renal cancer fighting drugs, i.e. Proleukin and alfa interferon, have been unsuccessful. In other words, each specific combination of two or more anti-cancer agents must be

tested before one of skill in the art can know that such combination will be effective against cancer, let alone more effective than either agent alone. The Examiner has failed to show otherwise.

Underscoring the unpredictability of success when combining two anti-cancer agents is U.S. Patent No. 5,597,830 (previously submitted), wherein the inventors demonstrate that there are limitations to combination therapy and that anti-cancer agents such as taxol and other taxanes are actually *inhibited* by the oncolytic agent Suramin (see col. 4; Figure 3; and Figure 6).

Accordingly, the Examiner has failed to establish the *prima facie* obviousness of claims 19 and 28 over these references.

In view of the above remarks, applicants maintain that claims 19 and 28 satisfy the requirements of 35 U.S.C. §103(a) and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Claim Rejections Under 35 U.S.C. §112, First Paragraph

The Examiner rejected claims 19, 28 and claim 30 under 35 U.S.C. §112, first paragraph. The Examiner concedes that the specification is enabling for a method of treating prostate cancer in a subject in need of such treatment wherein said prostate cancer overexpresses HER-2/neu comprising administering to the subject therapeutically effective amounts of humanized monoclonal antibody that is *selective* for the extracellular domain of the Her-2/neu protein. However, the Examiner asserted that the specification allegedly does not provide enablement for the method set forth in claims 19, 28 and 30, wherein said

humanized monoclonal antibody is *specific* for the extracellular domain of the Her-2/neu protein. The Examiner stated that the specification does not enable any person skilled in the art to which it pertains or with which it is most nearly connected to practice the invention commensurate in scope with these claims.

The Examiner stated that the claims are drawn to said method with any antibody that binds to the extracellular domain or Her-2/neu regardless of whether it cross reacts with other antigens including EGF receptor. The Examiner asserted that one cannot extrapolate the teaching of the specification to the scope of the claims because it is well known in the art, as previously set forth in the February 3, 2005 Office Action (pages 5-6), that HER-2/neu is a member of the EGFR family and shares homology with other members of the family. The Examiner further asserted that given the shared homology, it would be expected that antibodies that were not selective for HER-2/neu would cross react with and be sequestered by, other members of the EGFR family. The Examiner asserted in particular, that it is known that anti-tumor antibodies must accomplish several tasks to be effective. The Examiner stated that they must be delivered into the circulation that supplies the tumor and interact at the proper site of action and must do so at a sufficient concentration and for a sufficient period of time. The Examiner also stated that the target cell must not have an alternate means of survival despite action at the proper site for the anti-tumor antibody. In addition, variables such as biological stability, half-life or clearance from the blood are important parameters in achieving a successful therapy. The Examiner stated that the antibody may be inactivated *in vivo* before producing a sufficient effect, for example, by degradation, immunological activation or due to an inherently short half life of the antibody. The Examiner stated that the

antibody may not otherwise reach the target because of its inability to penetrate tissues or cells where its activity is to be exerted, may be absorbed by fluids, cells and tissues where the antibody has no effect, circulation into the target area may be insufficient to carry the antibody and a large enough local concentration may not be established. The Examiner asserted that this is critical when considering the homology of HER-2/neu to the EGFR family.

The Examiner stated that the specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the broadly claimed method will function as claimed with reasonable expectation of success.

The Examiner stated that applicants' prior argument has been considered but has not been found persuasive because claim 19 was amended to recite that the antibody is "specific" for Her-2/neu protein, not selective. The Examiner stated that in particular, Roitt et al,(*Immunology*, 1993, Mosby, St. Louis, p 6.4-6.5) teaches that when the determinants of antigen A are shared by another antigen, B, then antibodies that bind to those determinants in A will also react with B. The Examiner stated that this phenomenon is termed cross-reactivity(see Fig. 6.8 on page 6.4 and p. 6.5, para 1), thus antibody that "binds specifically" to Her-2/neu will also bind specifically to other proteins of the EGFR family that share the same determinants.

The Examiner also stated that while claim 19 is enabling for therapy of androgen-dependent prostate cancer with anti-Her-2/neu antibody alone for the reasons set forth in the specification,

pages 87-96, the claims read on the treatment of all prostate cancers (including the claimed androgen-independent prostate cancer) with said antibody alone and the specification does not support the breadth of this claim. The Examiner stated that if applicants were able to overcome the rejection set forth above claims 19 and claim 30 would still be rejected under 35 U.S.C. §112, first paragraph, because the specification allegedly does not reasonably provide enablement for said method comprising treating all prostate cancers with humanized monoclonal antibody that binds the extracellular domain of the Her-2/neu protein alone. However, the Examiner conceded that the specification is enabling for a method of treating *androgen-independent* prostate cancer in a subject in need of such treatment wherein said androgen-independent prostate cancer overexpresses HER-2/neu comprising administering to the subject therapeutically effective amounts of humanized monoclonal antibody that binds the extracellular domain of the HER-2/neu protein in combination with paclitaxel.

The Examiner stated that the specification does not enable any person skilled in the art to which it pertains or with which it is most nearly connected to practice the invention commensurate in scope with these claims.

The Examiner stated that the claims are drawn to a method of treating prostate cancer/androgen-independent prostate cancer in a subject in need of such treatment wherein said androgen-independent prostate cancer overexpresses HER-2/neu comprising administering to the subject therapeutically effective amounts of humanized monoclonal antibody that binds the extracellular domain of the HER-2/neu protein. The Examiner stated that this means the treatment with HER-2/neu antibody alone. The Examiner stated that

the specification teaches the immunohistochemically identified membrane overexpression of HER-2/neu in primary prostate cancer samples, see pages 87-96, and further teaches the treatment, in pre-clinical models, of cell-line derived androgen-independent sublines of CWR22 with the known, effective HER-2/neu antibody, HERCEPTIN. The Examiner stated that the specification teaches that no effect of HERCEPTIN on tumor growth was observed in any of the androgen independent tumors (p. 103, lines 16-17). The Examiner stated that when paclitaxel was given to animals with independent tumors, there was growth inhibition in each group. The Examiner stated that paclitaxel and HERCEPTIN cotreatment led to greater growth inhibition than was seen in the agents individually (para bridging pages 103-104).

The Examiner concluded that one cannot extrapolate the teaching of the specification to the scope of the claims because the specification clearly teaches that HERCEPTIN alone, the successful anti-HER-2/neu antibody cancer therapeutic, had no effect on tumor growth. The Examiner stated that given the specification's clear demonstration of lack of effect of HERCEPTIN alone, the claimed invention is not enabled.

In response to the Examiner's rejection of claim 30, but without conceding the correctness thereof, applicants note that this claim has been cancelled without prejudice or disclaimer. Thus, the rejection thereof is moot.

In response to the Examiner's rejection of claims 19 and 28, applicants respectfully traverse, noting that claim 19, as amended, addresses the issues set forth above by the Examiner. Applicants contend that claim 19, as amended, and claim 28, which depends therefrom, satisfy the enablement requirement of 35

U.S.C. §112, first paragraph, and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

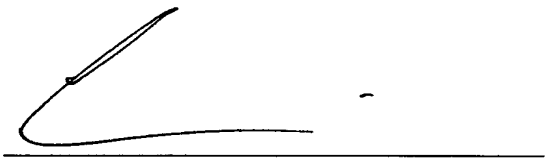
Summary

For the reasons set forth hereinabove, applicants respectfully request that the Examiner reconsider and withdraw the various grounds of rejection and earnestly solicit allowance of the pending claims.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone them at the number provided below.

No fee, other than the enclosed $60.00 fee for a one-month extension of time, is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,



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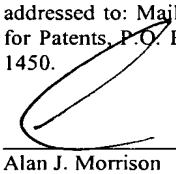

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Date